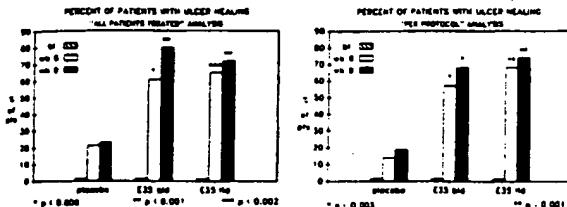


● ENPROSTIL (E) HEALS NSAID INDUCED GASTRIC ULCERS. S.J. Sontag, T.G. Schnell, E. Mak, K. Adelman, R. Fleischmann, S. Roth, K. Schwartz. Dept. of Ambulatory Care and Medicine, VA Hospital, Hines, IL; Dallas, TX; Phoenix, AZ; Syntex Research, Palo Alto, CA.

Conventional ulcer therapy is not effective in healing NSAID induced gastric ulcers (GU) or erosions (GE) if NSAIDs are continued. To determine whether a prostaglandin analog is an effective treatment for such lesions, we conducted a 9 week double-blind trial comparing placebo (PBO) vs enprostil 35 mcg bid (E35-bid) vs enprostil 35 mcg tid (E35-tid). Use of antacids was not allowed. Three centers entered 144 rheumatoid and osteoarthritis patients, mean age of 63 years, who required continuous fixed dose NSAID therapy. The minimum entrance criterion was the presence of 4 GE or one GU less than 5mm. GE was a break in the mucosal epithelium with exudate; GU was an erosion of at least 3mm in diameter with appreciable depth. Endoscopy was performed at weeks -2 and 0 to establish a stable pre-treatment baseline, and at weeks 6 and 9 during treatment. Results. All groups were similar in regards to age, sex, weight and height. 92 of the 144 patients (64%) had ulcers, most of which were GU; 52 had only GE. The "healing rates" (complete healing of all ulcers) of the 92 patients with GU are shown in figure 1 (all patients treated analysis).



The PBO, E35-bid and E35-tid ulcer healing rates were 21%, 61% and 65% at 6 weeks and 23%, 80% and 72% at 9 weeks. The healing rates were similar in the group of patients who met all protocol requirements (per-protocol analysis; figure 2). Thus, 1 in 4 PBO patients as compared with 3 in 4 E35 patients had complete healing of GU at 9 weeks (E-bid vs PBO,  $p \leq 0.006$ ; E-tid vs PBO,  $p < 0.001$ ). Additional GE and GU developed in 16% of PBO patients but in none of the E patients. 16% of E patients withdrew early from the study due to adverse experiences.

We conclude: 1) E35-bid and E35-tid are equally effective and superior to PBO in healing NSAID induced GU during continued NSAID therapy; 2) E heals GU and GE while protecting the mucosa against further NSAID-induced gastric injury.

● PIETAL CELL SENSITIVITY TO HISTAMINE IN HEALTHY VOLUNTEERS AFTER A 4-WEEK TREATMENT WITH ENPROSTIL AND RANITIDINE. J-C Soulé\*, C. Moulin\*, C. Dutreuil\*, L. Ory-Lavallée\*\* - \*Service de Gastro-entérologie, Hôpital Henri Mondor, 94010 Crétteil, \*\*Laboratoire Syntex, 20 rue J. Jaurès, 92800 Puteaux - FRANCE

Parietal cell sensitivity is increased in patients with active duodenal ulcer. It has been shown to increase in healthy volunteers after a 4-week treatment with Cimetidine and in patients with healed duodenal ulcer after a long-term treatment with Ranitidine. Retrospective meta-analysis have indicated that time to first relapse was longer after ulcer healing with Prostaglandins (PGs) than after healing with H2-receptor blockers, which might be due to a different effect of the two treatments on parietal cell sensitivity. This prompted us to study, in healthy volunteers, basal gastric acid secretion, acid secretory responses and parietal cell sensitivity to histamine before and after a 4-week treatment with Enprostil (E) and Ranitidine (R).

This was a randomized double-blind double-dummy crossover study. Twelve male healthy volunteers (22-44 years) were randomly assigned to receive a 4-week treatment with either E (35 mcg bid) or R (150 mg bid). After a 2-month washout period, they were crossed over to the alternate treatment. Basal acid output (BAO), acid secretory responses to a low-dose histamine infusion (histamine dihydrochloride 2.5 mcg/kg/h) (LDAO), to a high-dose histamine infusion (25 mcg/kg/h) (HDAO) and parietal cell sensitivity (PCS = LDAO/HDAO x 100) were measured 24h before the first administration and 72h after the last administration of each medication.

Results. All secretory parameters were similar before treatment with E and R. As compared to pre-treatment values: a) BAO and HDAO tended to increase after both treatments (NS). b) LDAO slightly increased after R ( $18.5 \pm 9.0$  vs  $13.9 \pm 11.3$  mEq) but not after E ( $12.5 \pm 6.3$  vs  $13.2 \pm 6.6$  mEq). c) PCS was unchanged after R ( $0.36 \pm 0.1$  vs  $0.33 \pm 0.2$ ) but decreased after E ( $0.30 \pm 0.2$  vs  $0.36 \pm 0.2$ ;  $p < 0.02$ ). When secretory parameters after treatment with R and treatment with E were compared, the difference was significant for LDAO ( $p < 0.02$ ) and PCS ( $p < 0.05$ ).

Conclusion. In healthy volunteers, parietal cell sensitivity to histamine was unchanged following 4 weeks of treatment with R; it decreased following 4 weeks of treatment with E and was significantly lower than that after treatment with R. In patients with duodenal ulcer disease, this observation might be relevant to the lesser propensity of the ulcers to relapse early after healing with PGs than after healing with H2-receptor blockers.

● SOMATOSTATIN ANALOG STIMULATES INTESTINAL MIGRATING MOTOR COMPLEX ACTIVITY IN NORMAL VOLUNTEERS AND PATIENTS WITH PROGRESSIVE SYSTEMIC SCLEROSIS. H. Soudah, C. Owyang, Dept. of Internal Medicine, University of Michigan, Ann Arbor, MI.

Previous studies suggest somatostatin stimulates intestinal motility. We investigated the effects of the somatostatin analog octreotide (trade name Sandostatin) on fasting gastroduodenal motility in 6 healthy volunteers and 5 progressive systemic sclerosis (PSS) patients with intestinal dysmotility and bacterial overgrowth to determine if octreotide might have a therapeutic role. After fluoroscopic placement of a manometrics catheter, basal motility was recorded for 2 migrating motor complexes (MMC) in healthy volunteers or 4 hours in the PSS patients if no MMC activity was noted. Octreotide was given subcutaneously and motility was recorded for an additional 3 hours. Blood was drawn every 15 minutes for plasma motilin to assess the role of endogenous motilin in octreotide induced intestinal motility. Results: In healthy volunteers, octreotide (10  $\mu$ g) decreased intestinal MMC cycle length from  $120.8 \pm 21.2$  to  $43.1 \pm 3.1$  minutes ( $p < 0.013$ ) and decreased propagation velocity from  $10.9 \pm 0.5$  to  $6.6 \pm 0.3$  cm/min ( $p < 0.002$ ). The duration of phases I and II were markedly decreased, whereas phase III duration was unchanged. Contractile frequency and amplitude also were unchanged. In PSS patients, basal recording showed antral activity which was not propagated into the duodenum. Octreotide (30  $\mu$ g) induced intestinal MMC-like activity with a cycle length of  $49.1 \pm 4.9$  min and a maximal frequency of  $10.8 \pm 0.2$ /minute which was aborally propagated at  $11.1 \pm 0.3$  cm/min. The amplitude of contractions induced by octreotide in PSS patients was less than in volunteers ( $15.4 \pm 3.0$  vs  $32.7 \pm 2.2$  mmHg). In healthy volunteers, spontaneous phase III activity was associated with increased motilin levels compared to phase I ( $112.2 \pm 15.1$  vs  $91.7 \pm 11.1$  pM). Octreotide induced intestinal phase III activity without increasing plasma motilin ( $57.2 \pm 6.5$  pM). In PSS patients, octreotide-induced intestinal phase III activity was also associated with depressed plasma motilin compared to peak levels before octreotide ( $140.7 \pm 33.9$  vs  $229.4 \pm 33.1$  pM,  $p < 0.007$ ). In both groups, motilin remained low for at least 2 hours despite further MMC cycling. This suggests that octreotide stimulates intestinal MMC activity independent of motilin release. Conclusion: Octreotide decreases intestinal MMC cycle length and propagation velocity in healthy volunteers and stimulates propagative phase III-like intestinal activity in PSS patients. This is not due to enhanced release of motilin. Thus the somatostatin analog octreotide may serve a useful therapeutic role in patients with intestinal dysmotility.

● A PROSPECTIVE, RANDOMIZED TRIAL OF MEDICAL AND SURGICAL THERAPIES FOR GASTROESOPHAGEAL REFLUX DISEASE (GERD). S.J. Spechler, W.O. Williford, and The VA Cooperative Study Group #277.

We have compared the efficacy of medical and surgical therapies for GERD. From July 1986 to November 1988, 248 patients with one or more complications of GERD (Barrett's esophagus, ulceration, stricture, erosive esophagitis) were assigned randomly to one of three treatment groups, and were followed for at least one year. Anti-reflux life-style modifications and Maalox TC tablets prn for heartburn were prescribed for all study patients. Patients in the Continuous Medical group (77) received Maalox TC or Amphogal (2 tabs 1 and 3 h pc) and ranitidine (150mg bid) daily for the duration of the study; metoclopramide (10mg qid) and sucralfate (1g tid) were added in a stepwise fashion when necessary to control symptoms. Patients in the Symptomatic Medical group (88) received these same medications only when necessary for relief of symptoms. Patients in the Surgical group (83) were treated primarily with Nissen fundoplication. Treatments were compared on the basis of effects on three, prospectively defined, major outcome variables: 1) a symptom score index (GERD Activity Index [GRACI]), 2) the endoscopic grade of esophagitis (scale: 0 [best] to 3 [worst]), and 3) 24-hour esophageal pH testing. Results after one year of therapy:

	Surg.	Cont. Med.	Symp. Med.
GRACI Score	$111.1 \pm 2.2$	$118.8 \pm 1.8^*$	$121.6 \pm 1.8^*$
Esophagitis	$1.27 \pm .17$	$1.76 \pm .15$	$2.23 \pm .16^*$

Time pH<4/24h  $7.9 \pm 2.6\%$   $9.8 \pm 2.2\%$   $14.6 \pm 2.5\%$   
(All values mean  $\pm$  SEM, \* = significantly  $>$  Surg.)  
We conclude that, after one year, antireflux surgery is more effective than medical therapy in improving the symptoms and endoscopic signs of GERD activity.